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Original Research

COPD

Inhaled Corticosteroids and Mortality in COPD*

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Study objectives: **To assess the influence of inhaled corticosteroids (ICSs) on mortality in COPD patients, which is currently a controversial topic.**

Setting: **Manitoba Health maintains a population-wide research database that includes pharmaceutical information.**

Design and patients: **We examined mortality in people 90 to 365 days after hospital discharge for COPD, comparing those persons who received inhaled steroids within 90 days of hospital discharge with those who did not. Cox proportional hazards models were used with adjustments for other respiratory drugs, comorbidities, and physician visits before and after hospital discharge. We also compared mortality in patients who received inhaled steroids with those who received other respiratory drugs, but not inhaled steroids, and those who received neither. Using nested case control analysis, we examined the time of receipt of inhaled steroids in relation to fatal events.**

Results: **In people > 65 years of age, inhaled steroids were associated with a 25% reduction in mortality between 90 and 365 days after hospital discharge, while mortality increased with bronchodilator use, physician visits, age, and comorbidities. The exclusion of people who had also received a diagnosis of asthma or had received inhaled steroids before hospitalization did not change the result. Inhaled steroids were associated with an even larger mortality reduction in people aged 35 to 64 years. People who received bronchodilators but no steroids had higher mortality than people who received no bronchodilators or received both bronchodilators and inhaled steroids. The reduction in all-cause mortality was largely due to the decreased number of cardiovascular deaths. The receipt of inhaled steroids within 30 days of death was protective, but this was not the case for greater time intervals.**

Conclusions: **Therapy with ICSs reduced mortality in COPD patients; the effect was particularly notable for cardiovascular death and was short term in that it was dependent on recent exposure.**

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Key words: cardiovascular mortality; COPD; database analysis; mortality

Abbreviations: CI = confidence interval; HR = hazard ratio; ICD-9 = *International Classification of Diseases*, ninth revision; ICS = inhaled corticosteroid; OR = odds ratio

Several studies have examined the course of COPD patients to whom inhaled corticosteroids (ICSs) were prescribed.[1–6] In four studies,[1–3,6] ICSs were prescribed within 90 days after discharge from the hospital for a COPD exacerbation, which is a time of relative instability when the risk for hospital readmission or death is high and therapy with ICSs might be expected to be administered to high-risk patients. In such patients > 65 years of age who are treated with ICSs, the risk of death was reduced by 21% over 1 year of follow-up in Ontario[1,7] and 25% over 3 years of follow-up in Alberta.[2] In the United Kingdom, the unadjusted risk of death was reduced by 30% in COPD patients > 50 years of age.[3] On the other hand, there was no reduction in the 1-year mortality rate observed in patients > 55 years of age in Saskatchewan.[6] All-cause mortality over 3 years was also reduced in patients > 50 years of age in the United Kingdom who had received at least three prescriptions of fluticasone over the initial 6-month period.[4] Such a benefit was not found in the US study[5] and the Saskatchewan study[6] using either

intent-to-treat or time-dependent analysis. Our objective was to determine the effect of ICSs on total and cause-specific mortality in a cohort of COPD

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patients using the Province of Manitoba health research database.

Materials and Methods

Database

The Province of Manitoba provides universal health-care insurance for all its residents (approximately 1.1 million). For research purposes, the Manitoba Population Health Research Repository integrates anonymous records of all inpatient and outpatient physician contacts, vital statistics (for date and cause of death), and drug dispensation records. It is linked via an anonymous identifier to the Population Registry, which provides the duration of health insurance coverage for each permanent Manitoba resident; coverage ends when the resident stops living in the province or dies. Physician contacts are based on fee for service claims describing services provided and the diagnosis for which services are rendered. The Drug Programs Information Network database is created by provincial retail pharmacies entering drug dispensations in real time in order to facilitate screening for inappropriate use, such as drug interactions, and copayment for medication. It captures all dispensing of medications except for drugs given to patients in the hospital. The pharmaceutical database contains anonymous identifiers of drug recipients and information about the drug dispensed (*ie*, the anatomic therapeutic chemical code[8]; the drug identification number; the date and quantity dispensed; the number of days covered by the supplied medication; and cost).

Subjects

We identified all people who had been admitted to the hospital between April 1, 1996, and March 31, 2000, and had been discharged from the hospital with a primary diagnosis of COPD (*ie*, *International Classification of Diseases*, ninth revision [ICD-9], codes 490 [not otherwise specified bronchitis], 491 [chronic bronchitis], 492 [emphysema], and 496 [chronic airflow obstruction]).[9] Subjects had to be ≥ 35 years of age on hospital admission as well as permanent residents of the province for at least 1 year prior to hospital admission and 1 year after discharge from the hospital or until death.

Variables

The outcome variable was death from any cause in the 365 days following discharge from the hospital. We extracted the date and cause of death. The causes of death were derived from death certificates and were divided into the following three groups: COPD and asthma (ICD-9 code 493); cardiovascular (ICD-9 codes 390–459 and 798); and all other causes.[9]

Covariates: At the index hospital admission, we determined the age and sex of subjects, and the number of physician visits for COPD and asthma that had occurred in the year prior to hospital admission. Comorbidity was assessed using the Charlson comorbidity score derived from secondary hospital discharge diagnoses that were listed at the index hospitalization.[10] Dispensing records were obtained for ICSs, β-agonists, ipratropium bromide, theophyllines, antimicrobials, and oral corticosteroids in the year prior to the index hospital admission, as well as between discharge from the hospital and the end of the 1-year observation period or date of death, if this occurred first. Respiratory medication use other than ICSs and the number of physician visits were considered to be markers of disease severity.

Design

We excluded from the analysis patients who died within 90 days of hospital discharge to allow the remaining subjects an equal opportunity to receive therapy with ICSs. All were followed up for 1 year or until death. Analyses were performed separately for people 35 to 64 years old and for those > 65 years old. Two study designs were implemented.

In the cohort study, subjects who received at least one prescription for ICSs in the 90 days following hospital discharge were compared to those who did not with respect to the risk of death during the subsequent 275 days. In addition, subjects who did not receive ICSs were divided into those who received bronchodilators and those who did not. The three groups were compared with respect to the risk of death, with the bronchodilator group serving as a reference. Finally, analyses were repeated to compare the risk of dying from specific causes.

In a nested case-control analysis, subjects who died within 90 to 365 days of hospital discharge were compared with respect to ICS exposure before death (*ie*, the index date) to age-matched and gender-matched control subjects who had survived to the same point in time. It was thus possible for the same individual to be both a case patient and a control subject. We compared case patients and control subjects regarding the most recent receipt of ICS between hospital discharge and the index date. Exposure to ICSs was divided into the following five mutually exclusive groups: ICSs within 30 days; ICSs in 30 to 60 days; ICSs in 60 to 90 days; and ICSs in > 90 days prior to death or not at all. We repeated this analysis for deaths ascribed to COPD and to cardiovascular causes.

Statistical Analysis

Cox proportional hazard models were used to analyze the cohort study. Conditional logistic regression was used to analyze the nested case-control study. Both hazard and odds ratios (ORs) were adjusted for the effects of age, sex, Charlson comorbidity score, physician visits in the year prior to hospital admission, and medication received following discharge from the hospital. The 95% confidence intervals (CIs) were calculated for hazard ratios (HRs) and ORs. The results were considered statistically signif-

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icant if $p < 0.05$. For analysis, we used a statistical software package (SAS, version 8.2; SAS Institute; Cary, NC). The Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health approved the study.

Results

Of 5,491 people discharged from the hospital with a diagnosis of COPD from 1996 to 2000, 1,007 (18.0%) were 35 to 64 years old and 4,584 (82.0%) were older. Of subjects ≥ 65 years old, 562 (12.3%) died within 90 days and were excluded from the analysis. The remaining 4,022 subjects were divided into the following two groups: 1,629 subjects (40.4%) who received ICSs within 90 days of discharge from the hospital; and 2,393 subjects (59.5%) who did not (Fig 1).

Among 1,007 subjects between 35 and 64 years of age, 42 (4.1%) died within the first 90 days and were excluded from the analysis. The remaining 965 subjects were divided into the following two groups: 369 subjects (38.2%) who received ICSs within 90 days of discharge from the hospital; and 596 subjects (61.8%) who did not (Table 1).

The characteristics of subjects who were treated and not treated with ICSs are compared in Table 1. In both age groups, those subjects who received ICSs were more likely to receive other medications within 90 days following hospital discharge. During the year prior to the hospitalization, they visited physicians more frequently for COPD and asthma, and were more likely to be treated with respiratory drugs. Among subjects in the older group, treatment with ICSs was significantly associated with less comorbidity.

For subjects between 35 and 64 years of age, the mortality rate between 90 and 365 days was 3.3% in those treated with ICSs and 6% in those not treated with ICSs. The comparable mortality rate for subjects > 65 years of age was 11.7% in those treated with ICSs and 13.1% in those not treated with ICSs (Fig 1). Table 2 shows the effect of ICSs on mortality in the Cox model adjusted for the effect of selected covariates. In subjects > 65 years, ICS use was associated with a 25% reduction in mortality. The use of ipratropium and theophylline as well as age, sex, comorbidity, and the number of prior physician visits were all associated with an increased risk of death. In subjects 35 to 64 years of age, there was an even greater reduction in mortality (53%) in those subjects treated with ICSs.

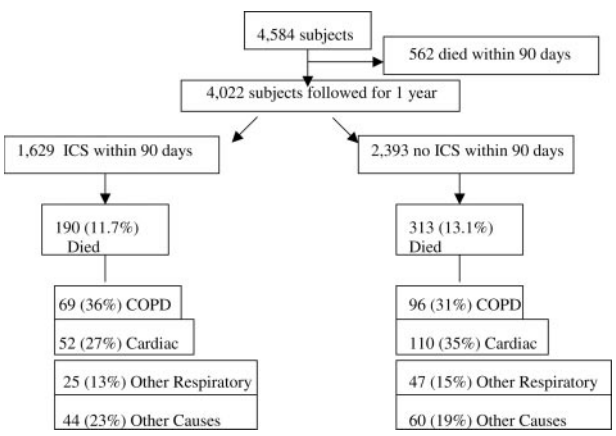

Figure 1. Flow chart of treatment of subjects ≥ 65 years of age who were hospitalized for COPD.

In the group of subjects ≥ 65 years, we repeated the above analysis after excluding all subjects who had a physician claim for asthma (n = 761) in the year prior to hospitalization. The reduction in mortality associated with ICS use was not affected (adjusted HR, 0.76; 95% CI, 0.61 to 0.95). Further, when all subjects who had received ICSs in the year prior to hospitalization (n = 1,718) were excluded, the reduction in mortality associated with ICS use after hospital discharge was even larger (adjusted HR, 0.66; 95% CI, 0.48 to 0.91).

In the cohort analysis, subjects were classified into ICS users and nonusers on the basis of drug dispensation in the 90 days following discharge from the hospital. Subsequently, the two groups differed substantially in terms of the receipt of ICSs; 79.5% of those classified as users at 90 days had filled a prescription for ICSs between 90 and 365 days after hospital discharge compared with 12.0% of nonusers. Each month, between 90 days and the 12th month, approximately 40 to 45% of ICS users received additional ICSs compared to 5 to 10% of initial nonusers.

Among subjects ≥ 65 years who were not treated with ICSs, 1,326 (55.4%) received bronchodilators (*ie*, β-agonists, ipratropium bromide, or theophylline) within 90 days following hospital discharge. Surprisingly, the remaining 1,067 subjects (26.5% of the total) did not receive bronchodilators, although they could have received antibiotics or oral corticosteroids. Only 7% of patients who received ICSs during the first 90 days after hospital discharge did not also receive bronchodilators. These patients and those who received only systemic steroids and/or antibiotics constituted groups that were too small for meaningful analysis. Between the 4th and the 12th month, approximately 60% of the ICS group, 55% of the bronchodilator group, and 10 to 15% of the no-treatment group filled a prescription for a bronchodilator. We repeated the Cox model comparing the following three treatment groups: ICSs; bronchodilators; and neither. We used bronchodilators as the reference treatment because this is currently

Table 1—*Characteristics of Patients Who Were Hospitalized for COPD by Receipt of ICSs Within 90 Days of Hospital Discharge

Characteristics	Patients 35–64 yr			Patients ≥ 65 yr		
	No ICSs (n = 596)	ICSs (n = 369)	p Value	No ICSs (n = 2,393)	ICSs (n = 1,629)	p Value
At index hospitalization						
Age, yr	54.5 ± 8.1	56.3 ± 6.9	< 0.001	77.7 ± 7.1	76.9 ± 6.8	< 0.001
Male sex, %	46	46	0.77	55	54	0.52
Charlson comorbidity score	0.32 ± 0.84	0.29 ± 0.71	0.88	0.53 ± 0.94	0.46 ± 0.93	0.004
One or more medications dispensed within 90 d of hospital discharge, %						
Inhaled β-agonists	40	90	< 0.001	48	89	< 0.001
Inhaled ipratropium	30	67	< 0.001	40	74	< 0.001
Oral corticosteroids	28	56	< 0.001	28	49	< 0.001
Oral antimicrobials	48	60	< 0.001	45	53	< 0.001
Oral theophyllines	7	17	< 0.001	9	19	< 0.001
Medication dispensed within 1 yr prior-hospitalization						
ICSs,%	20	59	< 0.001	24	71	< 0.001
Inhaled β-agonists, %	43	74	< 0.001	49	79	< 0.001
Inhaled ipratropium, %	23	43	< 0.001	35	59	< 0.001
Oral corticosteroids, %	23	38	< 0.001	23	38	< 0.001
Oral antimicrobials, %	64	75	< 0.001	64	75	< 0.001
Oral theophyllines, %	11	20	< 0.001	11	20	< 0.001
Office visits in the 1 yr prior-hospitalization	2.7 ± 4.2	5.0 ± 6.2	< 0.001	3.2 ± 5.0	4.8 ± 5.2	< 0.001

*Values are given as the mean ± SD, unless otherwise indicated.

recommended for all symptomatic COPD patients. Therapy with ICSs reduced the risk of death by 23% (95% CI, 6 to 37%) in comparison with bronchodilator treatment. Reduction was significant for cardiovascular deaths (38%; 95% CI, 11 to 57%) but not for COPD (Fig 2). Mortality reductions with ICSs were similar to those observed in patients who had received neither bronchodilators nor inhaled steroids. Presumably, this group of patients had less serious disease; in addition to their lower mortality rate and lower drug use, in the year prior to the initial hospitalization they had fewer physician visits for COPD (mean, 2.4 physician visits; patients subsequently given inhalers, 4.4 physician visits).

To ascertain the relationship between the length of time ICSs were used and mortality, we carried out nested case-control analyses examining a series of time frames. Subjects (n = 503) > 65 years of age who died within 90 to 365 days of hospital discharge were compared to age-matched and gender-matched control subjects who survived to the index date with respect to the timing of exposure to ICSs before the death of the case patient. Those who died (data not shown) had more comorbidities and physician visits, and received more prescriptions for respiratory medications other than ICSs than did control subjects.

In comparison of mutually exclusive time windows of 0 to 30 days, 30 to 60 days, 60 to 90 days, and > 90

Table 2— *Risk of Death in the 90–365 Days Following Hospital Discharge

Variables	Patients 35–64 yr	Patients ≥ 65 yr
Medications used within 90 d of hospital discharge		
ICSs	0.47 (0.23–0.98)	0.75 (0.61–0.91)
β-agonists	1.18 (0.54–2.57)	1.19 (0.93–1.53)
Ipratropium	0.95 (0.46–2.00)	1.26 (1.01–1.57)
Theophyllines	1.41 (0.60–3.34)	1.40 (1.10–1.79)
Antimicrobials	0.88 (0.49–1.58)	0.94 (0.79–1.13)
Oral corticosteroids	1.20 (0.62–2.32)	1.07 (0.88–1.30)
Age	1.07 (1.02–1.12)	1.04 (1.03–1.05)
Male gender	0.88 (0.49–1.59)	1.25 (1.04–1.50)
No. of visits in the 1 yr prior to hospitalization	1.02 (0.97–1.07)	1.03 (1.02–1.05)
Charlson comorbidity score	1.80 (1.56–2.07)	1.36 (1.29–1.44)

*Values are given as the adjusted HR (95% CI).

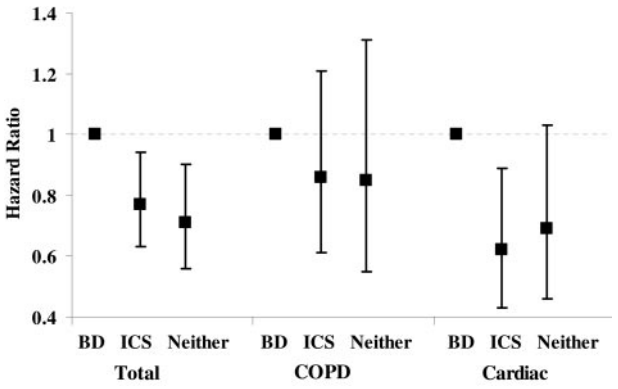

FIGURE 2. Risk of death (total and cause-specific) after 90 days in patients > 65 years of age who were segregated by treatment within 90 days of discharge from hospital. HRs with 95% CIs were adjusted for age, sex, number of physician visits in the year prior to hospitalization, and Charlson comorbidity score. The reference group was patients who were treated with bronchodilators (BDs) but not ICSs.

days prior to death, the receipt of ICSs < 30 days prior to death was significantly associated with reduced mortality from all causes (Fig 3). Further, ICS receipt within 30 days prior to death was associated with reduced numbers of deaths due to both COPD (adjusted OR, was 0.61; 95% CI, 0.41 to 0.91) and cardiovascular causes (adjusted OR, 0.54; 95% CI, 0.34 to 0.86) [Fig 3]. As Figure 3 shows, mortality associations weakened with longer intervals after the receipt of ICSs.

In order to determine whether the long-term use of ICSs was associated with a reduction in mortality, we repeated the case-control analysis by including only case patients (n = 322) and their control subjects who had survived for 6 months after discharge from the hospital. Those who died between 5 months and 1 year were compared to those who survived with respect to the use of ICSs and other drugs over 6 months preceding death. Again, only the receipt of ICSs within 30 days was associated with a reduced mortality from all causes (adjusted OR, 0.54; 95% CI, 0.38 to 0.75).

DISCUSSION

The main findings of our study were as follows: (1) in COPD patients > 65 years of age, ICS use after hospital discharge was associated with a 25% reduction in all-cause mortality that was not affected by excluding people with a previous diagnosis of asthma or previous ICS use; (2) a substantial reduction in mortality (approximately 50%) was also observed with ICS use in patients aged 34 to 65 years; (3) the reduction in mortality appeared to be largely ascribable to reduced cardiovascular mortality and to some extent mortality from COPD; (4) patients treated with ICSs had mortality that was comparable to those treated with neither bronchodilators nor ICSs and was lower than for those treated with bronchodilators, but not with ICSs; and (5) the effect of ICSs was most evident in the short term, most notably with drug receipt within the preceding 30 days.

Our study has a number of strengths. It examined a large unselected population of patients, including those < 65 years of age, using a comprehensive database. We attempted to assess and adjust for comorbidities and disease severity by examining the use of other respiratory drugs and physician expo-

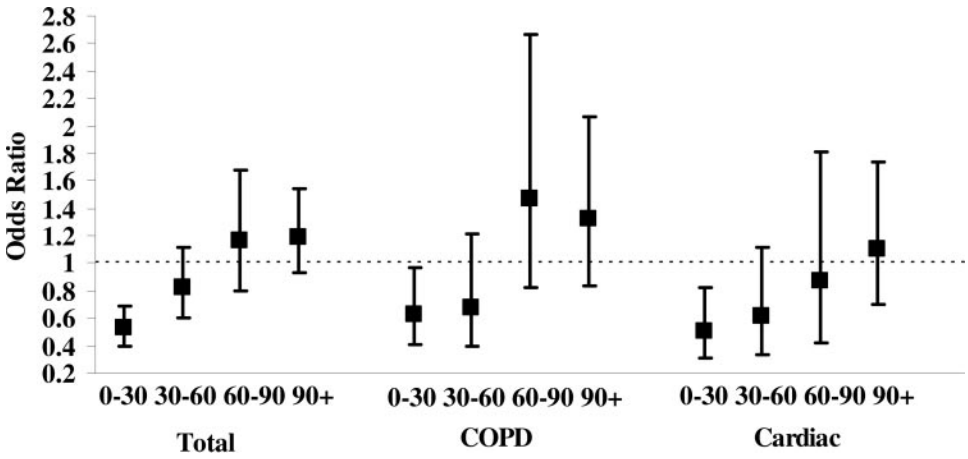

FIGURE 3. The ORs for death in subjects > 65 years of age depending on the timing of ICS use prior to death. ORs with 95% CIs are shown for overall, COPD, and cardiovascular mortality. They were adjusted for the number of prescriptions for β-agonists, ipratropium, oral theophyllines, antimicrobials, and oral corticosteroids that had been dispensed since hospital discharge as well as for age, sex, the number of physician visits in the year prior to hospitalization, and Charlson comorbidity score.

sure. Excluding patients with a previous diagnosis of asthma, or those who had previously used ICSs did not affect our results. We avoided immortal time bias[11,12] by excluding deaths within the first 90 days of hospital discharge. We were further able to examine mortality in relation to the timing of the receipt of ICSs.

There were no records of drug prescription during hospitalizations in our database, giving rise to two potential biases. First, people who were hospitalized in the initial 90 days of observation had less opportunity to receive outpatient medications such as ICSs and were potentially a high-mortality group. We repeated our analysis after eliminating people who were rehospitalized during the initial 90 days, and ICSs were associated with reduced mortality in the remainder (relative risk, 0.73; 95% CI, 0.58 to 0.92), so this issue did not confound our cohort analysis. A second potential bias concerns people dying in hospitals who had received unknown drugs, introducing an error in estimating the potential influence of outpatient prescriptions in regard to death. We repeated our case-control study examining only people who had not been hospitalized at death. The same relationships shown in Figure 3 were observed (*ie*, the effect of ICSs was most evident in the 30 days before death), so we do not think that this bias influenced our result in an important way.

Our study had limitations that are common to most database analyses. We relied on physician claims for diagnoses, which are often inaccurate, but are less so when derived from hospital discharge information as we did. We attempted to control for disease severity and comorbidities but cannot be certain that this was successful. We used drug dispensing as a surrogate for drug use and recognized that the two were not necessarily the same, although they were most likely to be similar immediately after drug receipt. Further, discrepancies between drug dispensing and use would have tended to blur the time effects associated with the former. We relied on death certificates to ascertain causes of death, which may have been misclassified but not biased with respect to treatment group. All-cause mortality data were robust, and the main causes of death (*ie*, COPD and cardiovascular disease) were consistent with the literature.[13,14]

The reduction in all-cause mortality that we found was of similar magnitude to that observed in other cohort studies[1,3,4,7] and was present in time-dependent analyses that were comparable to those that produced negative results.[5,6] Randomized trials of ICSs in COPD patients have not shown significant mortality effects, but pooled data from these trials have shown a mortality benefit of similar magnitude to ours.[15] We believe that it is likely that ICSs do indeed reduce mortality in COPD patients, but further evidence from randomized trials would be helpful in resolving the controversy.

Though death due to COPD itself tended to be reduced by ICS therapy, the effect was weaker than that on cardiovascular death. The relatively weak effect on death due to COPD was compatible with the results of several carefully done trials[16–19] showing that therapy with ICSs did not alter the rate of decline of lung function in COPD patients. In regard to cardiovascular mortality, our results are in agreement with reports[20,21] indicating that therapy with ICSs is associated with a decreased risk of myocardial infarction. The mechanism for the reduction in cardiovascular deaths associated with ICSs is not clear. Possible explanations include reductions in COPD exacerbations,[18] which produce hypoxia and instability that may predispose to cardiovascular events, reduction in systemic inflammation[22] or reduced adaptive immune response.[23,24]

COPD patients treated with bronchodilators and without ICSs had higher mortality rates than those treated with neither. This is compatible with bronchodilator use being a surrogate for disease severity; that is, people who received bronchodilators were sicker than those who did not. However, the fact that patients who received ICSs, who also received bronchodilators, had death rates that were similar to patients who received neither, might be interpreted as suggesting that ICSs reduced mortality by canceling a negative effect of bronchodilators. There is no evidence that bronchodilators increase all-cause mortality in COPD patients, but there have been several studies[14,25,26] that suggest that bronchodilators may increase the risk of cardiovascular events. It is thus possible that bronchodilator therapy is associated with cardiovascular events in COPD patients, and that ICSs negate or reduce this effect. Such an influence would be compatible with the evidence that the influence of ICSs on mortality appears to be a short-term effect that is best seen in the 30 days after the receipt of the agents.

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